Macrophage Colony -Stimulating Factor ("CSF"), Monocyte-Macrophage CSF, Granulocyte CSF, vascular epithelial growth factor ("VEGF"), Angiogenin, transforming growth factor alpha ("TGFα"), transforming growth factor beta ("TGFβ"), heat shock proteins, carbohydrate moieties of blood groups, Rh factors, fibroblast growth factor, chemotherapeutic drugs, AZT, nucleotides, DNA, RNA, sense, antisense, cancer cell specific antigens, hormones, and antibodies admixed with or bound to a colloidal metal.

REMARKS

The present invention is directed to compositions comprising a colloidal metal, such as colloidal gold, and one or more biologically-active factors. The biologically-active factors may be admixed with the colloidal metal particles or may be bound to the colloidal metal particles. In the compositions comprising target molecules, the target molecule may bind to a receptor on a cell membrane. The composition may also contain additional components such as excipients, buffers, antigen stabilizers, carriers, or adjuvants.

The present invention is also directed to methods for administering biologically-active factors to a human or animal by administering the compositions described above. Further, the present invention is directed to methods for treating cancer and immune diseases in humans and animals.

With entry of the present amendment, Claims 2-10, 15-26, 28-31, and 33-34 are pending in the application. Support for the claims as amended may be found throughout the specification and original claims. No new matter has been introduced by these amendments. No additional fees are believed due with the filing of the present amendment. However, the Commissioner is hereby authorized to charge any deficit, or credit any overpayment, to Deposit Account No. 10-1215.

Applicants appreciate the courtesy shown their representatives by Examiners Delecroix-Muirheid and Jones during the personal interview conducted on January 18, 2000. The present amendment incorporates those changes discussed during

the interview. Therefore, the claims as amended are believed to be patentable over the prior art of record.

Rejection of Claims 1-3, 5, 6, and 8 under 35 U.S.C. § 102(b) as anticipated by Shiosaka *et al.* (U.S. Patent No. 5,112,606)

The rejection of Claims 1-3, 5, 6, and 8, under 35 U.S.C. § 102(b) as anticipated by Shiosaka *et al.* made in the previous office action has been maintained.

Claim 1 has been canceled making the rejection moot with regard to that claim. As discussed during the interview, Shiosaka *et al.* does not disclose or suggest compositions comprising target molecules or methods of targeted delivery. Applicants appreciate the Examiners' indication that Claim 8 is not anticipated or rendered obvious by Shiosaka *et al.* Accordingly, Claims 2-7 have been amended to depend from Claim 8. Therefore, reconsideration and withdrawal of this ground of rejection is respectfully solicited.

Rejection of Claims 1, 9, 15, and 19 under 35 U.S.C. § 102(b) over Schienberg (U.S. Patent 4,487,780)

Claims 1, 9, 15, and 19 have been rejected under 35 U.S.C. § 102(b) as anticipated by Scheinberg. Claim 1 has been canceled; Claims 9, 15, and 19 have been amended to include a target molecule in the composition; and new Claims 33-34 have been added.

Scheinberg discloses a composition comprising a gold salt and a derivative of cysteine for the treatment of rheumatoid arthritis. Nowhere does Scheinberg disclose or suggest compositions comprising target molecules or mthods of targeted delivery. Therefore, Claims 9, 15, and 19 are not anticipated or rendered obvious by Scheinberg.

New Claim 33 is directed to the treatment of cancer. Nowhere does Scheinberg disclose or suggest the treatment of cancer. New Claim 34 recites the treatment of cancer or an immune disease with a specific list of biologically-active factors. None of these factors are disclosed or suggested by the Scheinberg patent.

Therefore, new Claims 33 and 34 are not anticipated or rendered obvious by Scheinberg. In light of the claim amendments and Applicants' remarks, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Rejection of Claims 1-4 under 35 U.S.C. § 102(b) over Ohmann *et al.*

Claims 1-4 have been rejected under 35 U.S.C. § 102(b) as anticipated by Ohmann *et al.* Claim 1 has been canceled and Claims 2-4 have been amended to depend from Claim 8, which was not rejected by the Examiner over the Ohmann *et al.* reference. Therefore, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Rejection of Claims 1-32 under 35 U.S.C. § 103(a) over WO 91/02078 in view of Scheinberg

Claims 1-32 have been rejected under 35 U.S. C. § 103(a) over WO 91/02078 in view of Scheinberg.

The Office Action states that "WO '078 discloses compositions comprising tumor necrosis factor-α (TNF-α) bound to a ligand that modulates the biological activity of the TNF by increasing the receptor binding activity and the cytotoxicity of TNF on tumor cells. The composition is used to treat tumors in individuals."

The Office Action further states that "WO '078 does not disclose binding the TNF with colloidal metal such as silver or gold; however, the Examiner refers to Scheinberg which discloses compositions comprising biologically active cysteine compounds in combination with gold or copper compounds. The compositions are administered to individuals for the purpose of treating rheumatoid arthritis. . . . Scheinberg discloses that the gold and silver [sic] particles serve to increase the efficacy of the cysteine compounds while lowering the dosage amount needed to treat rheumatoid arthritis."

Therefore, the Office Action alleges that "it would have been obvious to one of ordinary skill in the art to modify the method of WO '078 to administer compositions comprising TNF bound to colloidal gold or silver because such a

modification would have been motivated [by] the reasoned expectation of decreasing the dosage amount of TNF while at the same time increasing its efficacy in the treatment of tumors."

Applicants respectfully traverse this rejection for the following reasons. WO '078 discloses the use of antibodies or antibody fragments as ligands that specifically bind TNFα in a manner that the biological activity of TNF-α is modified. This modification is disclosed as an inhibition of TNF-α's activity to induce endothelial procoagulation and an enhancement of TNF-α's ability to induce fibrin deposition in tumors and to induce tumor regression.

Scheinberg discloses compositions containing gold or copper compounds with derivatives of cysteine, an amino acid. Scheinberg also discloses that the gold and copper compounds are useful for the treatment of rheumatoid arthritis by themselves. Further, Scheinberg discloses that the cysteine derivatives recited have a synergistic effect with the copper or gold compounds in the treatment of rheumatoid arthritis and that the disclosed compositions are less toxic than the use of other known treatments for rheumatoid arthritis, such as the use of penicillamine.

Applicants assert that there is no motivation, absent Applicants' disclosure, to combine these two references. WO '078 relates to the effect of a cytokine on tumors while Scheinberg relates to the use of an amino acid for the treatment of rheumatoid arthritis. While each reference employs a second ingredient, this ingredient is an antibody in the WO '078 reference and a metal compound in the Scheinberg patent. Additionally, the antibody in the WO '078 reference is employed as a ligand, i.e., it must be bound to the cytokine, whereas the metal compound of Scheinberg may simply be given in combination with the amino acid derivative.

Further, the second ingredients (the antibody fragment and the metal compound) modify the activity of the active substances (the cytokine and amino acid) in completely different ways. The antibody ligand changes the activity of TNF by inhibiting some of its properties and enhancing others. In contrast, the metal compounds of Scheinberg also have activity against rheumatoid arthritis and are used

with the active cysteine compound to create a synergistic effect, i.e. to enhance, not change, cysteine's activity.

Thus, is no motivation provided in either reference to substitute the antibody ligand of the WO '078 reference with the metal compound of the Scheinberg reference because the references describe different active ingredients, the treatment of different diseases, different modifying molecules (the antibody and colloidal metal), and different activities of the modifying molecules on the active ingredient.

During the interview with Applicants' representatives, the rationale for combining these references was discussed. Agreement was reached that the Claims are not rendered obvious by the combination of these references.

The Office Action further states that "with respect to claim 11, vaccination of an individual in the prior art would have been obvious in view of the fact that the method steps of the claimed invention and that of the prior art are substantially similar. While Applicants disagree with this rejection, Claim 11 has been canceled for reasons unrelated to the present rejection, rendering the rejection moot with regard to this claim.

Priority of the Application

In response to the Office Action issued March 17, 1999, Applicant's claimed priority to previous copending applications to overcome the Examiner's rejections based upon the published PCT application of those earlier applications. However, the claims as amended no longer read on the subject matter disclosed in that publication. Therefore, Applicants hereby disclaim the priority claimed in the response filed July 19, 1999. The specification has been amended to remove the priority data added in that response.

In light of the amendments and the above remarks, Applicants believe that Claims 2-10, 15-26, 28-31, and 33-34 are allowable over the prior art of record. Early and favorable consideration by the Examiner is solicited. If the Examiner believes any informalities remain in the application which may be corrected by Examiner's

Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 949-2400 is respectfully solicited.

Respectfully submitted,
JONES & ASKEW, LLP

By: Kimberly J. Prior
Reg. No. 41,483

2400 Monarch Tower
3424 Peachtree Road, N.E.
Atlanta, Georgia 30326
Telephone: (404) 949-2400
Facsimile: (404) 949-2499
J&A File: 01994-0024